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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/981,289	10/15/2001	Bassil I. Dahiyat	A-68990-3/RFT/RMS/RMK	5268

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05/19/2003

FLEHR HOHBACH TEST  
ALBRITTON & HERBERT LLP  
Four Embarcadero Center, Suite 3400  
San Francisco, CA 94111

EXAMINER

SEHARASEYON, JEGATHEESAN

ART UNIT

PAPER NUMBER

1647

DATE MAILED: 05/19/2003

18/5

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/981,289

Applicant(s)

DAHIYAT ET AL.

Examiner

Jegatheesan Seharaseyon

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 10 February 2003.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-3 and 13-16 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3 and 13-16 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 17. 6) ☐ Other: \_\_\_\_\_

**DETAILED ACTION**

1. This office action is in response to the amendment and response filed on 2/10/03 in Paper No: 15. Claims 1-3 and 13-16 are pending.
2. Applicant's correction of the specification is acknowledged.
3. Applicant's changing of the title is acknowledged.
4. It is noted that the Applicant has provided the corrections for Figures 8 and 9. The corrections required by the draftsman in PTO 948 are not present. Formal drawings provided by the Applicant have been approved by the draftsman.
5. The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office action.
6. The declaration provided by Dr. Robert Hayes under 37 CFR 1.132 filed 2/10/03 is sufficient to overcome the rejection of claims 1-3 and 13-16 based upon 35 USC § 112 1<sup>st</sup> paragraph as set forth in the last Office action of Paper No: 13 (see paragraph 8).

***Claim Rejections - 35 USC § 112 2<sup>nd</sup> paragraph, withdrawn***

7. Rejection of claims 1 and 16 as vague and indefinite under 35 USC § 112 2<sup>nd</sup> paragraph is withdrawn in view of Applicant's arguments filed on 2/10/03.

***Claim Rejections - 35 USC § 112 1<sup>st</sup> paragraph, maintained***

8. Applicant's arguments have been fully considered but are not persuasive. Thus the rejection of claims 1-3 and 13-16 under 35 USC § 112 1<sup>st</sup> paragraph for lack of written description and enablement is maintained. Applicant asserts that the disclosure is complete with relevant identifying characteristics to prove that the Applicant was in the possession of the claimed invention. However, Applicant in claiming the variant

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TNF- $\alpha$  protein does not refer to any sequence. In the absence of the recitation of a specific sequence, the skilled artisan cannot envision all the detailed chemical structure of the claimed polypeptides, regardless of the complexity or simplicity of the method of isolation.

With respect to the scope of enablement provision, Applicant fails to provide any guidance regarding a specific sequence contemplated. Furthermore, detailed information regarding the structural and functional requirements of the disclosed protein is lacking because there is no sequence recited. The specification as filed does not sufficiently teach one of skill in the art how to make and/or use the full scope of the claimed variant TNF- $\alpha$  proteins. The amount of experimentation required to make and/or use the full scope of the claimed invention would require trial and error experimentation to determine the functional sequences. Given the breadth of claims 1 and 16 in light of the unpredictability of the art as determined by the lack of working examples and shown by the prior art of record, the level of skill of the artisan, and the lack of guidance provided in the instant specification, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention. Claims 2, 3, 13, 14 and 15 are rejected insofar as they depend on claim 1.

***Claim Rejections - 35 USC § 102, maintained***

9. Claims 1-2 and 14-16 remain rejected under 35 USC § 102(b) as being anticipated by Banner et al. (U.S. Patent NO: 5, 597, 899) for reasons set forth in Paper No: 13.

Applicant's arguments filed on 2/10/03 have been considered but are not persuasive.

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Applicant asserts that the Office has mischaracterized the Banner reference and claims that the reference does not suggest, teach or disclose exchange between the mutants and wild type TNF-alpha to form mixed trimers. The Office relied on the Banner reference to teach the generation of the various TNF-alpha mutations with atleast one amino acid substitution. This reference teaches the preparation of mutations at several different amino acid positions compared to the wild-type TNF- $\alpha$ , which has different binding affinity to p55-TNF receptor compared to p75 TNF receptor Using standard molecular biology techniques (abstract). Amino acid substitutions have been made at 33, 34, 65, 67, 75, 143, 145 and 147, including the following changes: D143N, D143E, A145R and A145K (abstract and Tables I and II). It also teaches generation of multiple amino acid substitutions compared to wild-type TNF- $\alpha$  sequence, including at least 3 amino acid substitutions (columns 5 and 6). The formation of mixed trimers is a consequence of generating the mutants described in the prior art. Although Banner et al. may not have appreciated the trimer formation itself nonetheless meets the limitations of the instant claims in the teaching of the generation of various amino acid mutations. Despite the fact that applicants may have been the first to characterize the formation of mixed trimers, the formation of mixed trimers would inherently have occurred in the presence of the teachings of Bennett et al. mutants, which are similar to those of the instant invention. The Examiner notes the decision in *Swinehart and Sfiligoj*, 169 USPQ 226, in which it was found that mere recitation of a newly discovered function or property, inherently possessed by things in prior art, does not cause claim drawn to those things to distinguish over prior art. Although the prior art did not

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necessarily appreciate the mechanism of the formation of the trimers, it clearly teaches the same TNF-alpha mutants, as the rejected claims. Thus, claims 1-2 and 14-16 remain rejected under 35 USC § 102 (b) as being anticipated by Banner et al. (U.S. Patent NO: 5, 597, 899).

***Claim Rejections - 35 USC § 103, withdrawn***

9. Applicant's arguments have been fully considered and are persuasive. Thus rejection of claims 3 and 13 under 35 USC § 103(a) as being obvious over Banner et al. (U.S. Patent NO: 5, 597, 899) is withdrawn.

**New Grounds of rejection**

***Claim Rejections - 35 USC § 112, second paragraph***

10. Claims 1-3 and 13-16 are rejected as vague and indefinite for reciting the term "non-naturally occurring" is vague. Although the one of skilled in the art can clearly determine the variants compared to known TNF-alpha protein sequences (from for example: human, rat, mouse etc.), it is unclear how one would determine the non-naturally occurring proteins. It is possible that those sequences not normally present in human, rat, mouse etc. could possibly be present in other species because the art has not described all naturally occurring TNF-alpha proteins.

11. Claims 3, 14 and 15 are rejected as vague and indefinite for providing the species information of the TNF-alpha protein. In the absence of a reference to at least the species of origin, what does the residue number mean? Numbering is not an inherent property, and without reference to a specific protein, is meaningless.

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12. Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: It is not clear how the Applicant intends to recover a non-naturally occurring variant TNF-alpha.

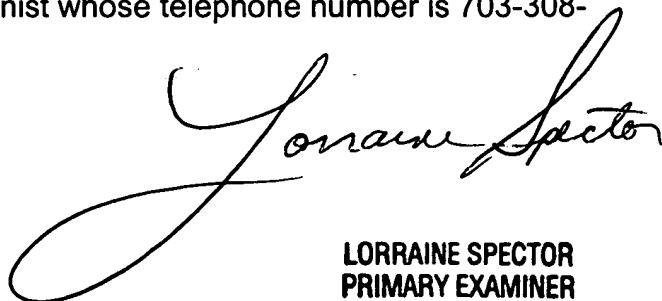
13. No claims are allowable. However, claims drawn specifically to substitutions at positions K112D, Y115T, D143K, D143R and Y115I of human TNF-alpha are free of prior art and allowable.

#### **Contact Information**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 703-305-1112. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-0294 for regular communications and 703-308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



LORRAINE SPECTOR  
PRIMARY EXAMINER